International Journal of Celiac Disease, 2016, Vol. 4, No. 4, 146-149
Available online at http://pubs.sciepub.com/ijcd/4/4/11

DOI:10.12691/ijcd-4-4-11

A 21-year-old Man with Delayed Puberty

Ketabimoghaddam Pardis[1], Dadvar Zohreh[2,*], Salehi Babak[3], Aletaha Najmeh[2], Allameh Seyed Farshad[2], Hassanpour Akbar[1], Talayi M.A[3]

[1]Arak university of medical sciences, Internal medicine department
[2]Tehran university of medical sciences,gastrointestinal department
[3]Shahid Beheshty university of medical sciences, gastrointestinal department
Tehran University of Medical Sciences, Iran
*Corresponding author: zohrehdadvar.zd@gmail.com

Abstract Delayed puberty is defined clinically by the absence or incomplete development of secondary sexual characteristics bounded by an age at which 95 percent of children of that sex and culture have initiated sexual maturation. The upper 95th percentile in the United States for age for boys is 14 (an increase in testicular size being the first sign) and for girls is 12 (breast development being the first sign). Delayed puberty pathophysiologically is classified according to the circulating levels of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in to two groups of high serum LH/FSH and low or normal serum LH/FSH concentrations which are related to primary hypogonadism and hypothalamic dysfunction respectively. *Patient Presentation.* A 21 year old boy presented with severe respiratory distress syndrome due to pneumonia and generalized edema. Laboratory studies showed pancytopenia which made clinicians work up for hematologic disorders, leading to bone marrow aspiration and biopsy which was consistent with megaloblastic anemia resulting from vit B12 deficiency. Another manifestation of this patient was delayed puberty which had been ignored over these years. Evaluation of delayed puberty revealed a low serum LH/FSH concentration. Accompaniment of delayed puberty resulting from hypothalamic origin with edema and hypoalbuminemia made clinicians work up for a malabsorption syndrome. Therefore upper endoscopy and colonoscopy were done and duodenal biopsies were consistent with celiac sprue. The unusual symptom of this patient was vit B12 deficiency which is rare in celiac disease. *Conclusion.* Neglected celiac sprue can be accompanied by vit B12 deficiency probably because of involvement of more distal parts of small intestine over the time.

Keywords: *delayed puberty, hematologic changes, celiac disease*

Cite This Article: Ketabimoghaddam Pardis, and Dadvar Zohreh, Salehi Babak, Aletaha Najmeh, Allameh Seyed Farshad, Hassanpour Akbar, Talayi M.A, "A 21-year-old Man with Delayed Puberty." *International Journal of Celiac Disease*, vol. 4, no. 4 (2016): 146-149. doi: 10.12691/ijcd-4-4-11.

1. Introduction

The patient was admitted in Arak Amir-Al-Momenin Hospital because of fever & chills, progressive dyspnea on exertion followed by orthopnea, paroxysmal nocturnal dyspnea, cough and black sputum during the past week and a progressive edema leading to generalized edema in recent year. He was born in the suburb of Arak city (one of the cities of Iran), in a low socioeconomic family, living with his mother, father and smaller brother. His childhood was spent with mild intermittent diarrhea (Soft stool sometimes watery but not bloody or fatty, without response to fasting, without significant abdominal pain), loss of appetite and failure to thrive. His immunization was complete. His adolescence was associated with delayed puberty, short stature and poor presentation at school. He was jobless, without any addiction to illicit drugs, alcohol and cigarettes. There wasn't any special disease or similar problem in his first degree relatives. No special environmental and occupational exposure was detected. Reported condition didn't make him demand a consult with healthcare units until he was encountered a progressive edema starting from lower limbs accompanied by scrotal, sacral, abdominal wall and periorbital edema during recent year with severe exacerbation in recent months and finally fever & chills and progressive dyspnea on exertion followed by orthopnea, paroxysmal nocturnal dyspnea, cough and sputum since the past week which took him to the emergency room. On the admission day, he was ill and cachectic, with pale conjunctiva, periorbital edema and severe exhaust. His vital signs were: Blood Pressure =125/85 mmhg, Body Temperature = 39.5oc, Pulse Rate = 140, Respiratory Rate = 34. Heart sounds were normal but tachycardia was detected. In lung auscultation there was a decrease in breath sound in the basis of the two lungs predominantly in the right side. Chest X Ray showed bilateral pleural effusion which was predominant in the right side. Abdominal examination showed positive shifting dullness test and abdominal wall edema without any tenderness and organomegaly. Deep and broad edema was detected in both lower limbs, distal pulses were bilaterally symmetric but were weaker than normal because of severity of edema. Scrotal examination revealed scrotal edema and small testicles. No axillary and

pubic hair was detected and his face was quite immature. The patient was admitted in general ward because of fever and tachycardia resulting in suspicion to severe inflammatory response syndrome due to pneumonia. Immediately, routine lab tests, blood cultures, urine analysis and culture, sputum smear and culture were sent to the laboratory. Then the patient received appropriate antibiotics for community acquired pneumonia; (Ceftriaxon + Azithromycin). Complete blood count results revealed pancytopenia: (White Blood Cells=1100 with differentiation results compatible with 30% polymorphonuclears and 69% lymphocytes, Hemoglobin= 6.9, Hematocrit= 22.5%, Mean Corpuscular Volume= 107, Platelets= 81000). Because of severe neutropenia (Absolute Neutrophil Count =330) and fever probably due to pneumonia, he admitted in an isolated room and went on wide spectrum antibiotics (Imipenem cilastatin), Granulocyte colony stimulating factor (300mg daily) and 2 units packed cell (Iso group and Iso Rh). Although pneumonia was probable in this patient because of fever and sputum but it seemed that some of his respiratory symptoms were explainable by generalized edema.

Therefore we decided to evaluate reasons of pancytopenia, anasarca, delayed puberty and diarrhea separately and altogether in this 21 year old man after release from recent crisis.

Before blood transfusion, blood samples were taken for serum Iron, Ferritin, TIBC, Folate and B12 level. Bone marrow aspiration and biopsy were taken.

The first important and gruesome abnormal finding in this patient was pancytopenia which made us worried about probable acute leukemia. Bone Marrow Aspiration is depicted in Figure 1. Sections showed bone trabeculae and intervening marrow spaces with cellularity of about 30%. A polymorphous population of hematopoietic cells was seen. Megakaryocytes were normal in number and morphology. On bone marrow aspirations, Megakaryocytes were adequate in number and have normal appearance. Erythroid cells showed megaloblastoid / dyserythropoietic changes including dissociation of cytoplasm/nucleus maturation, malnucleation and irregularity shaped nuclei. Some granulocytes have large granules and dysplastic nuclei. The differential count nucleated cells were as follows: blast = 2%, promyelocyte = 1%, myelocyte = 7%, metamyelocyte = 6%, band = 10%, erythroid = 50%, lymphocyte = 7%, eosinophil = 4%, plasmacells = 2%, monocytes= 1%. M/E ratio was about 0.7. These findings recommended further evaluation of combined deficiency (megaloblastic anemia + Iron deficiency anemia). Myelodysplastic syndrome also lied in differential diagnosis with lower probability. But Aplastic anemia, leukemias and other differential diagnoses became more impossible.

According to the results of BMA/BMB, this patient went on folic acid, B12 vitamin and ferrous sulfate regimen. Respiratory signs and symptoms improved with wide spectrum antimicrobial agent. No need to add anti staphylococcus or antifungal agents. Neutrophil count increased gradually, by GCSF, without any complication. The patient felt better over time. We were hoping that pancytopenia will be cured after treatment of megaloblastic anemia.

But there were still some questions about this patient; was there any relationship between delayed puberty and other sign and symptoms of this patient?

Our patient had 152 cm height, 48 kg weight, his arm span was 151 cm; compatible with under 3% percentile for height and weight with no secondary sex characteristics (testicles were palpable and compatible with stage 2 of tanner staging and pubic/axillary/chest and facial hair compatible with stage 3 of tanner staging). Particular attention also was paid to the symmetry of the testes as gonadal tumors can occur in several intersex disorders presenting at puberty with asymmetrical gonadal development and defects in sexual maturation. An x-ray of the left hand & wrist for evaluation of bone age was obtained to assess skeletal maturation. The X-ray revealed patent epiphyseal plates compatible with bone age of about 12. Random measurements of serum LH and FSH, together with testosterone was obtained to distinguish between primary and secondary hypogonadism which confirmed secondary hypogonadism by low levels of LH and FSH. High serum concentrations of LH and FSH are associated with various causes of gonadal disease, called primary hypogonadism and/or defects in their receptors on the membrane of the gonadal cells. Low or normal serum LH and FSH concentrations are associated with various causes of diminished GnRH-induced gonadotropin secretion, called secondary hypogonadism. Impaired secretion and/or action of hypothalamic GnRH typically is the underlying cause of secondary hypogonadism. It can be functional in origin (as in constitutional delay of puberty, chronic illness, excessive exercise, malnutrition, and stress) or related to associated pathology (as with hypothalamic and pituitary tumors, especially craniopharyngioma), or genetic causes (hypogonadotropic hypogonadism with anosmia [Kallmann's syndrome], or idiopathic hypogonadotropic hypogonadism [IHH]). Hypogonadotropic hypogonadism is the most common form. A complete history and physical examination should precede any biochemical testing or imaging study. [1] The history helps determine whether pubertal development is totally absent or had started but then "stalled." Thus, assessment of the patient's growth pattern up to the time of evaluation is critical. Patients with constitutional delay have delayed (not stalled) growth, adrenarche, and sexual development in temporal association with declining growth velocity, delayed skeletal maturation, and delayed adrenal androgen maturation. Other important issues in the history include: Nutritional habits, exercise intensity, prior medical illness, or medication usage that may delay the onset or slow the tempo of puberty. Delays in sexual maturation and growth velocity often can be the first clinical signs of underlying disorders, such as inflammatory bowel disease, hypothyroidism, or psychosocial deprivation. [2] The presence of associated congenital abnormalities (eg, midline defects, cryptorchidism, skeletal abnormalities like cleft lip/palate, or scoliosis) suggests congenital GnRH deficiency. [3]

A positive family history of either constitutional delay of puberty or congenital GnRH deficiency can be a useful clue. Indeed, delayed puberty has a significant genetic basis often demonstrating an autosomal dominant mode of inheritance, with or without incomplete penetrance. [3] The presence of an absent or abnormal sense of smell (anosmia or hyposmia) strongly suggests Kallmann syndrome, which is associated with a number of genes. Because of no history of delayed puberty in his family, probability of constitutional delay was low. A random

measurement of serum prolactin was obtained to detect hyperprolactinemia, which can present clinically as "stalled" puberty. But he didn't have stalled puberty and also he had normal levels of serum prolactin. Thyroid function tests for hypothyroidism, which can be responsible for delayed puberty of unknown mechanisms, was obtained and he had normal thyroid function test. Hormonal therapy with testosterone enanthate started because of severe pubertal delay and patient's psychosocial concern about this delay. Short term therapy with testestrone can result in induction of a growth spurt without inducing premature epiphyseal closure. This goal requires frequent (eg, every six months) longitudinal monitoring of bone age during therapy. The long-term goals of therapy, if the diagnosis proves to be isolated GnRH deficiency, are to maintain the serum concentrations of sex steroids within the normal adult range and, eventually, to induce fertility if and when the patient wants. [4] Further evaluation should have been directed at the possibility of nutritional disorders, occult chronic illness (eg, chronic inflammatory bowel disease, anorexia nervosa, or hepatic disease) that may affect the hypothalamic GnRH pulse generator, and hormonal abnormalities. Initial screening should include a complete blood count, erythrocyte sedimentation rate, blood urea nitrogen (BUN), creatinine, and liver function tests. Such an evaluation was important for our case because of history of intermittent diarrhea (Soft stool sometimes watery but not bloody or fatty, without response to fasting, without significant abdominal pain), loss of appetite and failure to thrive in his childhood. Hypocalcemia, hypoalbuminemia and hypoproteinemia without proteinuria, hypokalemia, hypophosphatemia and history of intermittent diarrhea in this patient made us search for malabsorption and its differential diagnoses. This patient went on a lactose free diet, which elicited in to some extent but not complete relieve of digestive system problem.

Transglutaminase Ab IgA was 98.6 (>18 is positive)

Abdominopelvic sonography and CT scan were normal and didn't reveal any sign of pancreatic calcification.

Upper and lower gastrointestinal endoscopy was done. Duodenal secretion was sent for evaluation of bacterial overgrowth syndrome which was negative. Biopsies were taken from duodenum and colon.

Duodenal sections showed completely flat with total villous blunting and crypt hyperplasia. There was increased number of mitotic figures in the crypts. There were dense inflammatory cell infiltration in the lamina propria with increased number of intraepithelial lymphocytes and plasma cells. Findings were consistent with celiac disease (CD) (Figure 2).

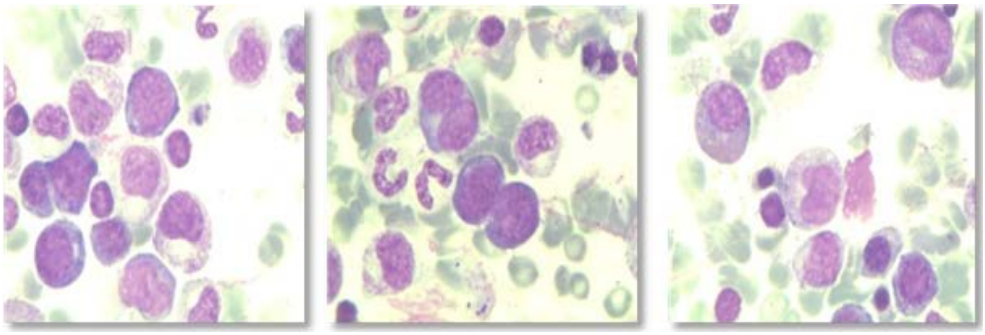

Figure 1. Megakaryocytes were adequate in number and have normal appearance. Erythroid cells showed megaloblastoid/dyserythropoietic changes including dissociation of cytoplasm/nucleus maturation, malnucleation and irregularity shaped nuclei. Some granulocytes have large granules and dysplastic nuclei

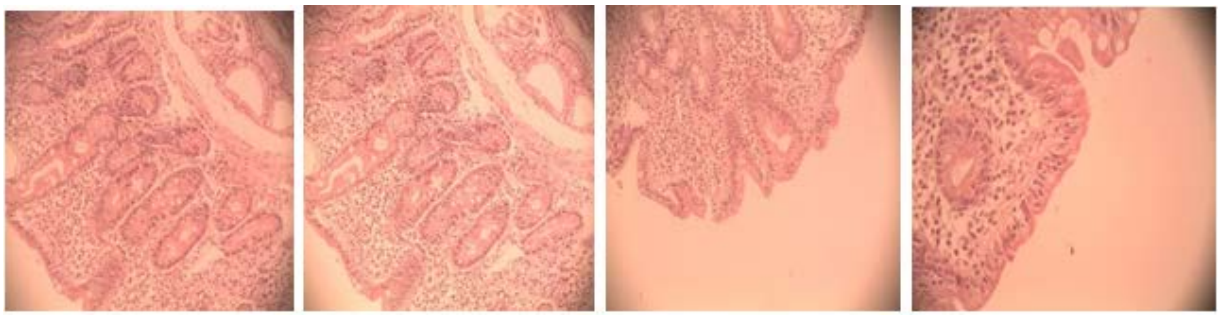

Figure 2. Duodenal sections showed completely flat with total villous blunting and crypt hyperplasia

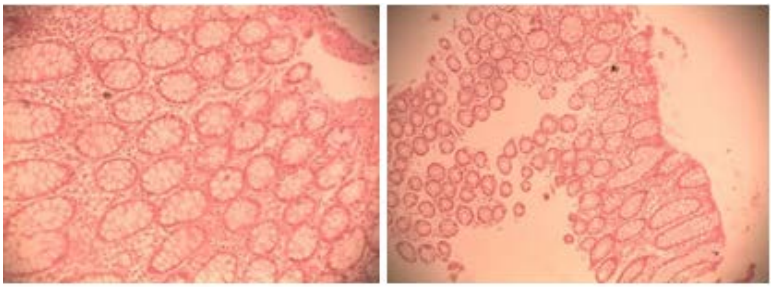

Figure 3. Colon sections presented regular glands and surface epithelium. The lamina propria was edematous and congested with mild increased inflammatory cells

Colon sections presented regular glands and surface epithelium. The lamina propria was edematous and congested with mild increased inflammatory cells. There was no evidence of malignancy in taken specimen. Findings were compatible with nonspecific colitis (Figure 3). Findings in CD (also called gluten-sensitive enteropathy and nontropical sprue) are mucosal inflammation, crypt hyperplasia, and villous atrophy. Unrecognized and untreated, CD is associated with increased mortality. [5]

Our patient went on gluten free diet (GFD), vitD and Ca supplements. After one month GFD, he had no longer diarrhea, got rid of generalized edema, felt improvement in respiratory function, sexual appearance and his appetite. After 6 month GFD he reported a weight gain about 10 kgs.

2. Discussion

It seems that our patient was a case of CD with typical and atypical sign and symptoms. Protein losing enteropathy [6,7,8] leading to edema, diarrhea, delayed puberty, iron deficiency anemia (transferrin saturation=17) [8,9] are well known in CD. But our patient had pancytopenia due to megaloblastic anemia of mixed folate and vit B12 deficiency which is not common in CD because of more proximal involvement of small intestine (responsible for iron and folate absorption) and sparing of distal parts of intestine (responsible for vit B12 absorption) in this disease. There are some papers working on hematologic disorders seen in celiac patients, but more studies are necessary to estimate the population of patients with CD presenting with pancytopenia due to megaloblastic anemia. [10]

3. Conclusion

Our patient had a long lasting CD with probable diffuse involvement of small intestine which can explain these mixed iron, folate and vit B12 deficiency leading to severe hematologic changes.

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